Cardiac Sarcoidosis: A Contemporary Concept of Forgotten Granulomatosis

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Abstract

Sarcoidosis is a complex multisystem inflammatory granulomatous disease that can affect any organ, with a wide range of clinical presentations. A significant number of patients with systemic sarcoidosis may also have cardiac involvement. Clinical manifestations of cardiac sarcoidosis can include various rhythm and conduction disturbances, as well as heart failure.

The structure of sarcoid granulomas is similar to that of tuberculous granulomas, but in contrast, they lack caseous necrosis. Tissue changes in sarcoidosis tissues depend on the stage of development of the disease, progressing from pathological process: macrophage-lymphocytic infiltration to epithelioid cell granuloma formation, and fibrosis. Granulomas can be found in any part of the myocardium, with the most common locations being the free wall of the left ventricle, the basal part of the interventricular septum, and the interatrial septum. Vasculopathy of the pulmonary circulation and coronary arteries is often observed.

Advancements in diagnostic imaging techniques, such as computer tomography and magnetic resonance imaging, have facilitated the verification of cardiac sarcoidosis. This article presents an analysis of updated information on cardiac sarcoidosis by a multidisciplinary working group.

Keywords: Sarcoidosis, Heart, Myocardium, Biopsy, Heart failure

Introduction

Sarcoidosis was a neglected problem in modern medicine and the healthcare system. The incidence of this disease is increasing around the world. Sarcoidosis has left the infectious units of phthisiatric institutions, increasingly debuting with cardiological, rheumatic, neurological, and other diseases, and therefore, the examination of patients must be mandatory in multidisciplinary clinics and comprehensive. The lung is no longer a monopoly organ of sarcoid granulomatosis. There are two general terms: cardiac sarcoidosis and isolated cardiac sarcoidosis.
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sarcoidosis. In the context of the presented review, the authors will discuss only updated international issues of cardiac sarcoidosis. Every new piece of information is of great interest because sarcoidosis is attracting the attention of an increasing number of clinicians and scientists. A chronic maladaptive immune response linking genetic susceptibility and specific infectious factors together with environmental factors is thought to be the causes of sarcoidosis. The infection factor in sarcoidosis is considered a trigger one since, in genetically predisposed patients, prolonged antigenic stimulation can lead to dysregulation of cytokine production, which is identified with an inadequate immune response. Infectious agents that cause sarcoidosis are non-tuberculous mycobacteria, Chlamydia pneumonias - the causative agent of pneumonia, Borrelia burgdorferi - the causative agent of Lyme disease, Propionibacterium acnes - bacteria, commensals of the skin and intestines of a healthy person, and certain species of viruses: Epstein-Barr virus, hepatitis C virus, cytomegalovirus, type VI herpes virus, JC virus (John Cunningham), and HTLV1 (Human T-lymphotropic virus type 1).

At the present stage, the concept of identifying the initiation of sarcoid granulomatosis is following that sarcoidosis cannot be a disease with a specific pathogen, while some researchers argue that an as-of-yet unidentified microorganism can be the causative agent of sarcoidosis. It is not solely caused by a single microorganism, and it is highly likely that multiple factors are involved.

In the overwhelming majority of cases, the target of lesion in cardiac sarcoidosis is the myocardium, which is clinically manifested as multiple arrhythmias and conduction disorders (from extrasystole to asystole), disorders of myocardial vascularization (from stable angina pectoris to postinfarction cardiomyopathy), as well as heart failure. These manifestations result from myocardial infiltration with granulomas and correlate with the degree of granuloma-associated disorganisation of the micro- and macrostructure of the intramyocardial parenchyma and stroma. Diffuse granulomatous alteration of the myocardium leads to a decrease in systolic function of the heart, however, if this indicator does not fall below 35%, then with timely maintenance therapy (pharmacological, hardware) and timely treatment of the underlying disease, normalization of the ejection fraction index can be achieved. Ventricular arrhythmias and sudden cardiac death are the main causes of death in patients with sarcoidosis. As a rule, arrhythmogenic lesions of the myocardium are associated with granulomatous infiltration in the areas of the cardiac conduction system's structural and functional components. With infiltration around the sinoatrial (SA) node, the SA node weakness pathognomonic syndrome occurs up to its complete shutdown, along with the characteristic clinical and electrophysiological manifestations. The excitability, as well as the automatism, are disturbed, which is clinically identified with episodic syncope and perisympov. When conducting daily ECG monitoring, one can often encounter a syndrome of migrating tachycardia and bradycardia (Short's syndrome). The complete atrioventricular (AV) block may occur, followed by asynchronous contraction with interference.

The mechanisms of the development of sarcoid granulomatosis are potentially involved in arrhythmogenesis through the development and progression of myocardial remodeling, ischemia, fibrosis, neurohumoral deactivation, electrolyte imbalance, and various channelopathies. In sarcoidosis, a complex of molecular, metabolic, and ultrastructural changes in cardiomyocytes and the extracellular matrix occur, causing an impairment of electrophysiological properties, which leads to structural changes in the myocardium. This is clinically manifested by a syndrome of electrophysiologically unstable myocardium. Multiple inflammatory phenomena are associated with arrhythmogenic myocardial damage. During the inflammatory process, hypoxia of cardiomyocytes occurs followed...
by HIF stimulation and thereby many growth factors with profibrotic activity. The changes in myocardium develop in parallel with this process. Thus, diffuse fibrosis occurs along with polyfocal fat deposition (from dusty to fine droplet type). Because of the difference in the properties of electrical conductivity of a healthy myocardium (striated cardiac muscle tissue), as well as adipose and fibrous tissues, a potential difference arises, which is clinically manifested by a high risk of developing multiple diffuse ectopic foci of the macro- and micro-re-entry type, i.e., there is a syndrome of electrophysiological unstable myocardium.

The profibrotic mechanisms involved in the onset and progression of myocardial fibrosis are not well understood, but the role of the renin-angiotensin-aldosterone system, transforming growth factor, inflammation, and the profibrotic effect of matrix metalloproteinases has been proven. Structural remodeling of the heart chambers destabilizes the electrophysiological homogeneity of the myocardium, thereby disrupting its conductivity and excitability, thus forming a substrate for maintaining arrhythmias. This process leads to the appearance of multiple ectopic foci, which favors the consolidation and preservation of arrhythmia. Electrophysiological remodeling favors an increase in the stability of arrhythmia during the first days after its onset, while there is a suppression of the incoming current of calcium ions through L-type channels and a shortening of the refractory period. Changes in the electrical and contractile properties of the atrial myocardium lead to a change in the volume and composition of the extracellular matrix and, as a result, to the development of myocardial fibrosis, which, in turn, contributes to the onset and maintenance of arrhythmia by a decrease in the elastic properties of the myocardium, in contractile function and pattern of coronary vasculature, which ultimately leads to the heart failure formation. Notably, patients with sarcoid heart disease have an increased risk of developing arrhythmogenic cardiomyopathy (dysplasia) of the myocardium, both left and right ventricles.

The course of cardiac sarcoidosis does not correspond to the process phases in the lungs. About a third of patients have heart damage in the background of mediastinal-pulmonary process. Cardiac sarcoidosis can manifest itself, masking other diseases, such as idiopathic cardiomyopathy, myocarditis, coronary artery disease, and coronary X-syndrome, making it difficult to confirm the diagnosis without endomyocardial biopsy, sometimes remaining beyond the possibility of morphological verification. The following are more often combined with heart damage: the second x-ray stage of the respiratory sarcoidosis and a presence of other extra pulmonary localizations (lesions of the skin, eyes, liver) are evident.

**Diagnosis**

There are fulminant (sudden cardiac death, infarction-like variant, cardiogenic shock), rapidly progressive (with increasing severity of manifestations to a critical level, for a maximum of 1 to 2 years) and slowly progressive (chronic, with relapses and remissions) variants of cardiac sarcoidosis. Independent predictors of a poor prognosis per the NYHA classification are the heart failure functional class III-IV, a critical increase in the LV end-diastolic size, and sustained ventricular tachycardia. Heart transplant cases of recurrent sarcoidosis have been reported.

**Diagnostics**

Sarcoidosis implies a fundamentally morphological approach to diagnosis, however, highly effective methods for diagnosing infiltrative myocardial lesions, such as magnetic resonance imaging (MRI), have now been proposed. However, the effectiveness of MRI is based mainly on statistical indicators of sensitivity and specificity, while to substantiate the place of MRI in the diagnosis of sarcoidosis, a careful comparison with morphological data, and diagnostic data of other infiltrative myocardial diseases is necessary.

**Morphological pattern**

Sarcoi d granulomas, as a rule, have no necrosis
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area, which is why they are called non-necrotic granulomas. However, some research groups provide some evidence that necrosis can be found, but it cannot be caseous. Also, it is critically vital to separate sarcoid reactions from sarcoid granulomas. Sarcoid granuloma characterized by cells of monocytic origin include macrophages, epitheloid, Pirogov-Langhans CD4+ T-lymphocytes, and fibroblasts. The Pirogov-Langhans cells are pathognomonic for sarcoid granuloma and have the form of crystals. Sometimes, it is possible to detect Schauman bodies with calcium and iron salts.

Radiation diagnostics
Sarcoidosis implies a fundamentally morphological approach to diagnosis, however, highly effective methods for diagnosing infiltrative myocardial lesions, such as magnetic resonance imaging (MRI), have now been proposed. However, the effectiveness of MRI is based mainly on statistical indicators of sensitivity and specificity, while to substantiate the place of MRI in the diagnosis of sarcoidosis, a careful comparison with morphological data, and diagnostic data of other infiltrative myocardial diseases is necessary. Characteristics of cardiac sarcoidosis are: small- or large-focal accumulation of contrast in the delayed phase on T1-weighted images (detection of cell necrosis or fibrosis), more often in the basal parts of interventricular septum. There is an increase in signal intensity on T2-weighted images. The chances of detecting the above signs are reduced on the background of corticosteroid therapy.

When performing positron emission tomography (PET), focal (mosaic) uptake of 18F-fluorodeoxyglucose and a decrease in the accumulation of 13N-ammonium (reflecting the “pseudo-ischemic” type of metabolism in the foci of active inflammation) are characteristic of cardiac sarcoidosis. Their severity decreases under the influence of GCS. The sensitivity of this method is much higher compared to other radionuclide methods. The sensitivity of endomyocardial biopsy does not exceed 30%, the reasons for which are: 1) “mosaic” location of granulomas in the myocardium (low percentage of accurate hit); 2) low accessibility of the most frequently affected areas (LV in general and its lower wall). One of the most promising methods for detecting cardiac sarcoidosis is cardiac magnetic resonance (MRI). An advantage of magnetic resonance is the ability to observe different phases of the myocardium. However, MRI semiotics in cardiac sarcoidosis are not specific and can be quite variable, as are the variants of the clinical pattern in the studied patients. Interpretation of symptoms requires sufficient qualifications of the MRI specialist and experience with this nosology. Because patients with cardiac sarcoidosis, for several reasons, do not often come to the attention of MRI specialists, such experience is limited, even though modern medical societies are discussing the possible justification of MRI and PET as the “gold” standard for diagnosing cardiac sarcoidosis.

The diagnosis of cardiac sarcoidosis must be considered excluded:

- Among young people with low cardiovascular risk, but with symptoms of heart failure;
- Cardiomyopathy and/or blockade of impulse conduction with a positive response to glucocorticosteroid and/or other immunosuppressive therapy;
- An inexplicable decrease in the LV ejection fraction of less than 40%;
- Unexplained sustained (spontaneous or induced) ventricular tachycardia;
- Idiopathic atrioventricular block II or III grade;
- Mosaic capture of 18F-FDG during PET myocardium;
- Delayed accumulation of gadolinium on MRI of the heart;
- Intramyocardial accumulation of 67Ga, the nature of which corresponds to cardiac sarcoidosis.

According to the recommendations of the Russian Society of Cardiology in 2019, the authors distinguish major and minor criteria.
**Major Criteria**
- AV blockade 2 or 3 grades in adults younger than 55 years, in combination with sustained monomorphic VT;
- Thinning of the basal segment of the interventricular septum;
- Increased absorption of the Ga67 isotope by the myocardium;
- Decrease in the EF index less than 50%.

**Minor Criteria**
- ECG: ventricular arrhythmias (VT, polyfocal or frequent PVCs), complete right bundle branch block, diffuse ST depression and/or ST elevation (up to 0.2).
- Echocardiography: focal disorders of wall contractility or structural changes in the myocardium (aneurysm, thickening or thinning of the left ventricle wall).
- Perfusion defect in myocardial scintigraphy with thallium201 or technetium99m isotopes.
- Presence of structural changes in the wall of the left ventricle and interatrial septum during MRI examination.
- Interstitial fibrosis or moderate infiltration on endomyocardial biopsy.

Heart involvement in sarcoidosis can be identified based on the following clinical features:
- If there are 2 or more major signs;
- If there is 1 major criterion and 2 or more minor criteria;
- If there are 3 or more minor signs.

Differential diagnosis is carried out with coronary artery disease, non-compact myocardium, idiopathic variant of dilated cardiomyopathy, toxic and infectious lesions of the myocardium, arrhythmogenic right ventricular dysplasia, etc.

**Laboratory diagnostics**
For an approximate assessment of the rheology of a sarcoid lesion, it is customary to use the following markers: soluble interleukin-2 receptor, neopterin, β2-microglobulin, chitotriosidase. An additional assessment can be given by the study of angiotensin-converting enzyme (ACE), C-reactive protein (CRP), as well as the concentration of calcium ions in the blood and urine.

The soluble interleukin-2 receptor (sIL-2R) is a fragment of a low-specific subunit of the membrane interleukin-2 receptor. Upon activation of T-lymphocytes and macrophages, sIL-2R is cleaved from the cell membrane. This marker may be used for monitoring transplant rejection. It may also be elevated in certain infections and autoinflammatory conditions (particularly periodic disease (Mediterranean fever)). Recently, this biomarker has been correlated with the degree of development of sarcoid granulomatosis. It is noted that a persistent decrease in the concentration of this biomarker is determined after the start of glucocorticosteroids (GCS) therapy and during the period of achieving remission. When comparing sIL-2R with CRP and ACE activity, sIL-2R alone predicts the severity of sarcoidosis.

There is also some evidence regarding neopterin. Among patients diagnosed with sarcoidosis, neopterin is found at higher levels and decreases as the disease resolves. The combined increase in the concentration of neopterin and sIL-2R is associated with an unfavorable prognosis and requires more aggressive corticosteroid therapy.

It is also necessary to mention that a study shows that among 123 patients with acute sarcoidosis and erythema nodosum with elevated levels of β2-microglobulin, an increase in ACE activity was recorded in only 43 patients.

Chitotriosidase is a macrophage activation biomarker that can be elevated in various lysosomal and non-lysosomal diseases, including Gaucher disease, Niemann-Pick disease, galactosialidosis, glycogenosis, malaria, thalassemia, and fungal infections, and serum levels serve as an indicator of the severity of sarcoidosis.

It should be noted that an increase in chitotriosidase is also observed in the development of sarcoid granulomatosis. The information content of this marker was 3 times higher than the values of ACE activity.

An increase in the IL-4/IL-2 index and...
a decrease in the level of IFN-γ serve as predictors of an unfavorable progressive course of the disease 3, 28.

**Cardiac Sarcoidosis: Treatment**

The goal of sarcoidosis treatment is to prevent or control organ damage as much as possible, as well as to alleviate organ-dependent symptoms and improve the patient's quality of life. Regardless of the form of manifestation of the disease, all patients are strongly recommended to conduct a comprehensive study, followed by a dynamic observation by the attending physician (immunologist, pulmonologist, rheumatologist, cardiologist, therapist, etc.). It should be considered that spontaneous remission (30-45%) is possible in sarcoidosis, but most often this phenomenon is observed in the acute variant of the course with an isolated lesion of the intrathoracic lymph nodes. There is no etiotropic therapy for sarcoidosis. In all cases, it is recommended to compare the need for treatment with the severity of the consequences from the use of corticosteroid, cytostatic or biological (“targeted”) therapy administration.

The treatment of cardiac sarcoidosis should be initiated as soon as the diagnosis is confirmed by a council or advisory committee 29, 30:

- Persistent and progressive processes in the heart failure unit. The treatment approach for cardiac sarcoidosis or cardiac involvement in systemic sarcoid granulomatosis is similar 29, 30.
- Progressive deterioration of external respiration;
- Persistent hypercalcemia and hypercalciuria.

Glucocorticosteroids (GCS) are the first-line drugs. In the absence of contraindications, all patients with an established diagnosis of cardiac sarcoidosis are recommended to take corticosteroids. Managing patients with cardiac sarcoidosis is an arduous task with many unknowns, the solution of which requires great responsibility, careful monitoring of the dynamics of clinical manifestations and the processing process activity, as well as the efficacy and safety of prescribed drugs.

Oral corticosteroids in most patients reduce systemic inflammation, thereby slowing down, stopping and sometimes even preventing organ alteration. GCS can be prescribed as monotherapy or in combination with other drugs.

The drug of choice is prednisolone. The recommended daily dose is 0.3-0.5 mg/kg (15-40 mg) per doses daily, for 1-3 months, for at least 9-12 months. When a positive effect is achieved, the prednisolone dose is reduced by 5 mg per month to a maintenance dose of 5-15 mg per day, for another 6-9 months until complete canceling 31-33.

Methotrexate is especially recommended for cardiac sarcoidosis 34. It is taken orally at a dose of 2.5-15 mg 1 per week, in the cases of resistance course, the dose can be elevated up to 25 mg 1 per week 34, 35. During the doses above 15 mg 1 per week, subcutaneous administration is more recommended. Monitoring of liver and kidney function every 1–3 months is highly recommended 36. If serum creatinine > 1.5 mg/dl (GFR < 50 ml/min), dosage adjustment or an alternative drug may be required for individuals with renal insufficiency. For side effects prevention, the folic acid administration in the dose mg in methotrexate free days is recommended.

Treatment with methotrexate should be interrupted when AST and ALT levels rise by more than 3 times, with subsequent resumption at a lower dose after laboratory parameters normalization. In each case, it is worth raising the question of the possible use of hepatoprotectors (low evidence). The use of methotrexate is contraindicated in women who are planning pregnancy, since methotrexate induces ovum necrosis. To minimize the side effects that occur during treatment with methotrexate, it is mandatory to take folic acid (5-10 mg/week), which should be prescribed no earlier than 24 hours after methotrexate intake.

According to the recommendations of the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) expert commission, methotrexate in the treatment of
sarcoidosis is considered as 37:
1. Second line drug with refractory to corticosteroids, with adverse reactions caused by steroids, and also to reduce the dose of a steroid;
2. A first-line drug as mono- or combined therapy with steroids (bridge therapy).
TNF-alpha inhibitors have been shown to be effective in reducing the symptoms of systemic sarcoidosis with cardiac involvement 31, 38-40.
Dosage modes:
• Infliximab – as an intravenous infusion, starts at 3-5 mg/kg, with loading doses at weeks «zero» (first injection), then second and six weeks, after which patients receive an infusion for 4-8 weeks.
• Adalimumab – preferably in the mode of “intermittent loading” of 120 mg in the first week and 80 mg in the second week. After this, switch to a dose of 40 mg per week.
Other treatment strategies: Due to cyclophosphamide its toxicity, it is usually indicated for the treatment of patients with severe sarcoidosis not controlled with corticosteroids, methotrexate, or in the case of limitations of TNF inhibitors administration. Studies have demonstrated that cyclophosphamide is effective in some patients with refractory manifestations of cardiac sarcoidosis 3, 39.
Mycophenolate mofetil, compared with placebo, shows positive results among patients with refractory sarcoidosis; it is a reserve therapy 3. Recommended doses in the presence of cardiac sarcoidosis are from 500 to 1500 mg 2 times a day 40, 41.
Tofacitinib is a selective inhibitor of the Janus kinase (JAK) family and an activator of the STAT protein. Studies have shown this drug’s effectiveness in treating refractory forms of permanent ventricular tachycardia 42.
In certain situations, individuals with cardiac sarcoidosis may require a cardiac defibrillator to prevent sudden cardiac arrest or manage heart rhythm abnormalities. Healthcare professionals evaluate various factors to determine the risk of life-threatening arrhythmias, such as the presence of heart tissue scarring or abnormal electrical conductance. They also consider the patient's medical history, symptoms, and the severity of the cardiac sarcoidosis. If the risk of sudden cardiac arrest is high, a cardiac defibrillator may be recommended to protect against sudden death. In some cases, cardiac sarcoidosis can cause issues with the heart’s conduction system, necessitating both pacing and defibrillation capabilities in a defibrillator. The decision to insert a cardiac defibrillator is based on a thorough assessment of individual circumstances and the risk of life-threatening arrhythmias. Collaboration between cardiologists, electrophysiologists, and other specialists is crucial to tailor the treatment approach to the specific needs of each patient.
A cardioverter-defibrillator is recommended for patients with life-threatening ventricular arrhythmias. Notably, systemic corticosteroid therapy normalizes myocardial conduction and excitability, however, in some patients, ectopic foci remain active for up to 6 months from the start of successful treatment of sarcoidosis. Therefore, the risk of destabilization of the rhythm and conduction of the heart also remains and increases whenever the dose of the administered drug is reduced 43-48.

Conclusion

Patients with severe heart failure should be considered for a heart transplant. However, cases of recurrent sarcoidosis have been reported.

Prognosis
Cardiovascular risk must be calculated using the SCORE2 scale 49, 50. All patients must be assessed regarding possible comorbidities, for example, diabetes-related cardiovascular injury 51-55, history of chemotherapy intake 56, thyroid gland pathology 57, oral cavity inflammation 58, helicobacter pylori infection 59, human immunodeficiency viruses 60 and other viruses related inflammation 61. The level of high sensitive troponin 62 and apolipoprotein(a) 63, Nt-pro-BNP 64 can provide supplementary information regarding
the state of cardiovascular health in cardiac sarcoidosis patients. Independent predictors of a poor prognosis are heart failure III-IV functional class by NYHA classification, as well as critical increase in the LV end-diastolic size, and resistant ventricular tachycardia. Summarizing the above facts, the authors can draw the following conclusions:

- Sarcoidosis has transformed into multiorgan, multisystem granulomatosis with an unpredictable course;
- To screen the potential involvement of the heart in the continuum of sarcoid granulomatosis, all patients with sarcoidosis are recommended to conduct ECG and echocardiography studies;
- The importance of creating a donor base, its improvement and increase in availability is noted, since with refractory current forms of cardiac sarcoidosis, heart transplantation is, although radical, but an effective method of treatment despite the long postoperative and recovery period.

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